



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2021-D-1051]

### Clinical Pharmacology Considerations for Antibody-Drug Conjugates; Draft Guidance for Industry; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice of availability.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Clinical Pharmacology Considerations for Antibody-Drug Conjugates,” which provides recommendations for the development of antibody-drug conjugates (ADCs). Specifically, this guidance addresses the FDA’s current thinking regarding clinical pharmacology considerations and recommendations for ADC development programs, including bioanalytical methods, dose selection and adjustment, dose- and exposure-response analysis, intrinsic factors, QTc assessments, immunogenicity, and drug-drug interactions (DDIs). Currently, there are no FDA guidances outlining the clinical pharmacology considerations for antibody-drug conjugates. This draft guidance is not final nor is it in effect at this time.

**DATES:** Submit either electronic or written comments on the draft guidance by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

**ADDRESSES:** You may submit comments on any guidance at any time as follows:

#### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions:* All submissions received must include the Docket No. FDA-2021-D-1051 for "Clinical Pharmacology Considerations for Antibody-Drug Conjugates." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:  
<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or to Office of Communication, Outreach and Development, Center for Biologics Evaluation and

Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

**FOR FURTHER INFORMATION CONTACT:** Kimberly Maxfield, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 209903, 301-348-1978, Kimberly.Maxfield@fda.hhs.gov; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

**SUPPLEMENTARY INFORMATION:**

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Clinical Pharmacology Considerations for Antibody-Drug Conjugates.” An ADC is a type of therapeutic biologic product that is composed of a small-molecule moiety and an antibody moiety conjugated together by a chemical linker. An antibody or antibody fragment carrier is selected or engineered against a specific antigen of interest present on the target, which is ideally unique to the disease state being treated (e.g., a tumor-specific antigen). In general, when the antibody or antibody fragment binds to its target antigen, the ADC is internalized through physiological mechanisms (e.g., endocytosis), at which point the small-molecule drug or payload moiety is released either upon exposure to the low pH of the lysosome or by degradation of the antibody/linker by lysosomal enzymes. The released small-molecule drug then exerts its effect in the targeted cell (e.g., the cells expressing the specific antigen of interest) while, ideally, minimizing the effect on healthy cells (e.g., cells that do not express the specific antigen of interest).

ADCs combine the selectivity of an antibody or antibody fragment with the potency of a small molecule. Therefore, development of ADCs requires careful consideration of the

differences between the clinical pharmacology of the antibody or antibody fragment and the small molecule. This draft guidance addresses FDA's current thinking regarding clinical pharmacology considerations and recommendations for ADC development programs, including bioanalytical methods, dose selection and adjustment, dose- and exposure-response analysis, intrinsic factors, QTc assessments, immunogenicity, and DDIs. Although this draft guidance is primarily based on FDA's experience with ADCs for oncology indications, the principles discussed in this guidance are also generally applicable to the development of ADCs for other indications.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Clinical Pharmacology Considerations for Antibody-Drug Conjugates." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

## II. Paperwork Reduction Act of 1995

While this draft guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information for submissions of investigational new drug applications, new drug applications, and biologic license applications in 21 CFR parts 312, 314, and 601 have been approved under OMB control numbers 0910-0014, 0910-0001, and 0910-0338, respectively. In addition, the submission of prescription drug labeling under 21 CFR 201.56 and 201.57 has been approved under OMB control number 0910-0572. The collections of information in 21 CFR part 211 have been approved under OMB

control number 0910-0139; and the collections of information regarding good laboratory practice in 21 CFR part 58 have been approved under OMB control number 0910-0119.

### III. Electronic Access

Persons with access to the internet may obtain the draft guidance at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <https://www.regulations.gov>.

Dated: February 1, 2022.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*

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